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| 10/584,303 | 04/05/2007 | Peter R. Brink | 13533/48103 | 9822 |

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| EXAMINER | |
|---|---|
| HA, JULIE | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/584,303 | BRINK ET AL. | |
| | Examiner | Art Unit | |
| | JULIE HA | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *2,8,10-11,13-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,9,12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Amendment after Non-final office action filed on February 24, 2010 is acknowledged. Claims 1-34 are pending in this application. Applicant elected with traverse of Group I (claims 1-12) and the species of nucleic acid that Cx43 and the corresponding polypeptide encoded by a nucleic acid that encodes Cx43 in the reply filed on August 14, 2009. The traversal was not found to be persuasive.

The requirement was deemed proper and was made FINAL in the previous office action. Claims 2, 8, 10-11 and 13-34 remain withdrawn from further consideration. A search was conducted on the elected species, and prior art was found. Claims 1, 3-7, 9 and 12 are examined on the merits in this office action. After further review, a non-final rejection follows.

### *Withdrawn Rejection*

1. Rejection of claims 1-7 and 9 under 35 U.S.C. 103(a) as being unpatentable over Taheri et al (US Patent No. 6,690,970, filed with IDS) in view of Pittenger et al (US Patent No. 6,387,369, filed with IDS), is hereby withdrawn in view of further review of the prior arts. A new rejection follows below.

2. Rejection of claims 1-7, 9 and 12 under 35 U.S.C. 103(a) as being unpatentable over Taheri et al (US Patent No. 6,690,970, filed with IDS) in view of Pittenger et al (US Patent No. 6,387,369, filed with IDS) and further in view of Donahue et al (US 2002/0155101 A1), is hereby withdrawn in view of further review of the prior arts. A new rejection follows below.

***Maintained and Revised Rejection***

***35 U.S.C. 112, 2nd***

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 6-7, 9, and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 6 recites, "The method of claim 1, further comprising a step of adding a gene to the mesenchymal stem cells by 35 electroporation." It is unclear what is encompassed within the term "gene". Gene encompasses promoters, enhancers, and regulators and other factors, therefore, it is unclear what is encompassed within the term "gene". Because claims 7, 9 and 12 depend from indefinite claim 6 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

***Response to Applicant's Arguments***

6. Applicant argues that "the term '35' has been deleted from claim 6, so the rejection should be withdrawn."

7. Applicant's arguments have been fully considered but have not been found persuasive. Applicant did not respond to the indefiniteness of the term "gene". Gene encompasses promoters, enhances, and regulators and other factors, therefore, it is unclear what is encompassed within the term "gene". Because claims 7, 9 and 12

depend from indefinite claim 6 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

***New Rejection***

***35 U.S.C. 102***

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1, 3-7 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Taheri et al (US Patent No. 6,690,970).

10. Taheri et al teach a biological pacemaker and implantation catheter for restoring normal or near normal heartbeat function without a mechanical pacemaker. The biological pacemaker is provided by a bridge of implantation cells, that are introduced into an area of electrical malfunction, such as an impaired SA node or a blocked AV node (see abstract). The reference teaches that the implantation cells can be introduced into the malfunction area in any suitable fashion, but are preferably injected via an

improved catheter that can be used for both node mapping and cell implantation (see column 3, lines 13-16), implantation cells introducing of about 200 picoamps and 700 picoamps of electricity to SA or AV node cells and this can cause them to dedifferentiate to their original embryonic form (see column 5, lines 1-8). The reference teaches growing mesenchymal stem cells in vitro, and then attaching one end of the strip onto the atrium of the heart (see Figs 3-5). Since the Figure 3 shows in vitro growth of stem cells, and Figures 4-5 show newly formed bridge across the area of AV node, this would be necessarily in a strip (according to the node). This meets the limitation of instant claim 1. The reference teaches that the implantation cells are either conduction cells obtained from a well-matched homologous AV node (or SA node) donor or autologous cardiac condution cells that have been cultured (see column 5, lines 10-13), meeting the limitation of claim 5. The reference teaches that additional implantation cell options include mixing or transvecting a gene that expresses connexin 43 protein with existing SA or AV node cells (see column 5, lines 23-25), meeting the limitation of claims 3-4, 6-7 and 9. The reference teaches the use of mesenchymal cells treated with connexin 43 and electrically stimulated in culture (electroporation) to form connections prior to implantation at the AV node (see column 5, lines 43-52), meeting the limitation of claims 1 , 3-6, 9. Therefore, the reference anticipates instant claims 1, 3-7 and 9.

11. Claim1, 3-7 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Rosen et al (US 2004/0137621).

12. The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

13. Rosen et al teach a composition for delivery of a gene to a syncytial structure comprising stem cells incorporated with the gene (see abstract). The reference teaches mesenchymal stem cells, such as human mesenchymal stem cells, as vehicles for gene delivery to syncytial structures, and ion channel genes can be delivered via stem cells to the cardiac region to alter cardiac pacemaker activity, to increase pacemaker current, or change membrane potential of the cells (see paragraph [0006], [0029], [0080], [0081] and [0091]). The reference teaches growth of mesenchymal stem cells *in vitro* and adding a gene to the mesenchymal stem cells by electroporation (see paragraphs [0114]-[0119], [0196], for example), meeting the limitation of instant claims 3-6. The reference teaches adding connexin 43 gene to the stem cells (see paragraphs [0142], [0199]), meeting the limitation of instant claims 7 and 9. The reference teaches an example of human mesenchymal stem cells transfected with HCN2 pacemaker gene implanted into the anterior left ventricular wall of the dog and shows that the pacemaker functions in canine ventricle *in situ* (see for example, paragraph [0029]). The reference teaches that the goals of phase 4 are to grow stem cells for transformation into a cardiac cell line, to select the cardiac cell lineage(s), to further induce the cardiac-like

cells to differentiate into ventricular or nodal cell types, and to transfect each of the individual cell types with appropriate genes to optimize function and survival in particular cardiac region (see paragraph [0144]). Furthermore, the reference teaches that cell lines engineered by phase 4 will provide bypass tracts that have the same function as the atrioventricular (AV) node in the heart *in situ* (see paragraph [0173]). Since the reference teaches all of the active method steps of instant claims, the reference anticipates instant claims 1, 3-7 and 9.

***35 U.S.C. 103***

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1, 3-7, 9 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taheri et al (US Patent No. 6,690,970, filed with IDS) in view of Donahue et al (US 2002/0155101 A1).

18. Taheri et al teach a biological pacemaker and implantation catheter for restoring normal or near normal heartbeat function without a mechanical pacemaker. The biological pacemaker is provided by a bridge of implantation cells, that are introduced into an area of electrical malfunction, such as an impaired SA node or a blocked AV node (see abstract). The reference teaches that the implantation cells can be introduced into the malfunction area in any suitable fashion, but are preferably injected via an improved catheter that can be used for both node mapping and cell implantation (see column 3, lines 13-16), implantation cells introducing of about 200 picoamps and 700 picoamps of electricity to SA or AV node cells and this can cause them to dedifferentiate to their original embryonic form (see column 5, lines 1-8). The reference teaches growing mesenchymal stem cells in vitro, and then attaching one end of the strip onto the atrium of the heart (see Figs 3-5). Since the Figure 3 shows in vitro growth of stem cells, and Figures 4-5 show newly formed bridge across the area of AV node, this would

be necessarily in a strip (according to the node). This meets the limitation of instant claim 1. The reference teaches that the implantation cells are either conduction cells obtained from a well-matched homologous AV node (or SA node) donor or autologous cardiac condution cells that have been cultured (see column 5, lines 10-13), meeting the limitation of claim 5. The reference teaches that additional implantation cell options include mixing or transvecting a gene that expresses connexin 43 protein with existing SA or AV node cells (see column 5, lines 23-25), meeting the limitation of claims 3-4, 6-7 and 9. The reference teaches the use of mesenchymal cells treated with connexin 43 and electrically stimulated in culture (electroporation) to form connections prior to implantation at the AV node (see column 5, lines 43-52), meeting the limitation of claims 1 , 3-6, 9. The difference between the reference and the instant claims is that the reference does not teach adding alpha and accessory subunits of L-type calcium channel.

19. However, Donahue et al teach methods of treating cardiac arrhythmia (see abstract). The reference teaches that genes that could be used to affect arrhythmias include ion channel and pumps (a-subunits or accessory of the following: potassium channels, sodium channels, calcium channels, chloride channels, stretch-activated cation channels…) or genes for proteins that affect the expression, processing or function processing of these proteins (see paragraph [0108] for example).

20. Therefore, it would have been obvious to one of ordinary skill in the art to add in genes or accessory subunit that would affect arrhythmias in the atrioventricular bypass tract for a heart. Donahue teaches that genes that could be used to affect arrhythmias

include ion channels and pumps that include α -subunits or accessory of calcium channel. Additionally, Taheri teaches transfecting mesenchymal stem cells with genes, such as connexin, and suggests adding new gene to promote the formation of gap junctions, which are essential for electrical connection to existing myocardial cells. Donahue further teaches that combining at least one polynucleotide encoding K channel subunit, Na channel subunit, Ca channel subunit, and a connexin to modulate electrical property of the heart (see for example, paragraph [0044]). There is a motivation to combine since Taheri et al teach that gene that expresses connexin 43 protein would serve to promote the formation of gap junctions, which are essential for electrical connection to existing myocardial cells (see column 5, lines 23-27), and Donahue teaches that α-subunits or accessory of calcium channel affect cardiac arrhythmias. Both Taheri and Donahue teach improving the function of the heart, thus, one would be motivated to combine sodium channel gene, calcium channel gene, or potassium channel gene with connexin gene in the mesenchymal stem cells. One would be motivated to combine in order to alter cardiac pacemaker activity, such as increasing pacemaker current, or to change membrane potential of the cells disclosed by Taheri et al. The MPEP states the following: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together

two conventional spray-dried detergents were held to be prima facie obvious.). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). But see In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive....Appellant argues... hindsight reconstruction or at best,... obvious to try'.... We agree with appellant."). There is a reasonable expectation of success, since connexin is serve to promote the formation of gap junctions, which are essential for electrical connection to existing myocardial cells and $\alpha$-subunits or accessory of calcium channel affect cardiac arrhythmias, combining the two known for the same purpose would at least have an additive affect.

21. Claims 1, 3-7, 9 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenet al (US 2004/0137621) in view Donahue et al (US 2002/0155101 A1).

22. Rosen et al teach a composition for delivery of a gene to a syncytial structure comprising stem cells incorporated with the gene (see abstract). The reference teaches mesenchymal stem cells, such as human mesenchymal stem cells, as vehicles for gene delivery to syncytial structures, and ion channel genes can be delivered via stem cells to the cardiac region to alter cardiac pacemaker activity, to increase pacemaker current, or change membrane potential of the cells (see paragraph [0006], [0029], [0080], [0081] and [0091]). The reference teaches growth of mesenchymal stem cells *in vitro* and adding a gene to the mesenchymal stem cells by electroporation (see paragraphs [0114]-[0119], [0196], for example), meeting the limitation of instant claims 3-6. The reference teaches adding connexin 43 gene to the stem cells (see paragraphs [0142], [0199]), meeting the limitation of instant claims 7 and 9. The reference teaches an example of human mesenchymal stem cells transfected with HCN2 pacemaker gene implanted into the anterior left ventricular wall of the dog and shows that the pacemaker functions in canine ventricle *in situ* (see for example, paragraph [0029]). The reference teaches that the goals of phase 4 are to grow stem cells for transformation into a cardiac cell line, to select the cardiac cell lineage(s), to further induce the cardiac-like cells to differentiate into ventricular or nodal cell types, and to transfect each of the individual cell types with appropriate genes to optimize function and survival in particular cardiac region (see paragraph [0144]). Furthermore, the reference teaches that cell

lines engineered by phase 4 will provide bypass tracts that have the same function as the atrioventricular (AV) node in the heart *in situ* (see paragraph [0173]). The difference between the reference and the instant claims is that the reference does not teach adding alpha and accessory subunits of L-type calcium channel.

23. However, Donahue et al teach methods of treating cardiac arrhythmia (see abstract). The reference teaches that genes that could be used to affect arrhythmias include ion channel and pumps ($\alpha$-subunits or accessory of the following: potassium channels, sodium channels, calcium channels, chloride channels, stretch-activated cation channels…) or genes for proteins that affect the expression, processing or function processing of these proteins (see for example, paragraph [0108]).

24. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Rosen and Donahue, since both references teach improving the function of the heart. It would have been obvious to one of ordinary skill in the art to combine sodium channel gene, calcium channel gene, or potassium channel gene with pacemaker gene, or to combine sodium channel gene with connexin gene, L-type calcium channel gene, or potassium channel gene, in the mesenchymal stem cells, because Rosen teaches transfecting human mesenchymal stem cells with polynucleotide encoding HCN2 or mutant HCN2, and connexin, and suggests adding new gene to optimize cell survival. Donahue teaches combining at least one polynucleotide encoding a K channel, Na channel, Ca channel, and a connexin to modulate electrical property of the heart. One of ordinary skill in the art would try various locations of the cells expressing the pacemaker ion channel in order to optimize the

effect of the pace maker ion channel on the heart function. One of ordinary skill in the art would be motivated to combine, in order to alter cardiac pacemaker activity, such as increasing pacemaker current, or change membrane potential of the cells as taught by Rosen et al or to modulate electrical property of the heart as taught by Donahue et al with a reasonable expectation of success. The MPEP states the following: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). But see In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to

optimize the amount of each additive....Appellant argues... hindsight reconstruction or at best,... obvious to try'.... We agree with appellant."). There is a reasonable expectation of success, since connexin is serve to promote the formation of gap junctions, which are essential for electrical connection to existing myocardial cells and $\alpha$-subunits or accessory of calcium channel affect cardiac arrhythmias, combining the two known for the same purpose would at least have an additive affect.

***Conclusion***

25. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654